Exhibit 1

UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
TECHNOLOGY CENTER (1600)

Dkt #873-Z-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Ivan C. KING, and Li Mou ZHENG
U.S. Serial No.	: 10/738,423
Confirmation No.	: 8783
Filed	: December 16, 2003
Art Unit	: 1633
Examiner	: Qian Janice Li
For	: COMPOSITIONS AND METHODS FOR TUMOR-TARGETED DELIVERY OF EFFECTOR MOLECULES

Law Offices of Albert Wai-Kit Chan, LLC
World Plaza, Suite 604
141-07 20th Avenue
Whitestone, NY 11357

March 29, 2007

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT IN RESPONSE TO THE DECEMBER 14, 2006 FINAL OFFICE ACTION AND PETITION FOR ONE-MONTH EXTENSION OF TIME

This communication is in response to the Final Office Action mailed on December 14, 2006. The shortened period for response expires on March 14, 2007. Applicants hereby request a one-month extension of time under 37 CFR 1.136(a). The fee for a one-month extension of time is SIXTY DOLLARS ($60.00) for a small entity. Applicants hereby authorize the Examiner to charge the full amount for the corresponding fee for the ONE MONTH EXTENSION OF TIME to Deposit Account No. 50-1891. The deadline to file a

response is now April 14, 2007. Accordingly, this communication is being filed in a timely manner.

Claim Amendment Fee Calculation

	Claims remaining after amendment		Highest No. Previously Paid	Extra	Rate (Large Entity)	Rate (Small Entity)	Additional Fee
Total	7	-	12	0	X $50.00	X $25.00	$0.00
Ind.	1	-	4	0	X $200.00	X $100.00	$0.00

Amendment to the claims begin on page 3 of this communication

Remarks begin on page 4 of this communication

Amendment(s) to the claims:
This listing of claims will replace all prior versions and listings of claims in the application:

1.-112. (Canceled)

113. (New) A method of inhibiting the growth or reducing the volume of a solid tumor cancer, comprising administering to a subject having a solid tumor cancer an effective amount of cytoxan or cisplatin and an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an attenuated tumor-targeted bacteria.

114. (New) The method of claim 113 wherein the attenuated tumor-targeted Salmonella further comprises an msbB$^-$ Salmonella mutant.

115. (New) The method of claim 113 wherein, the solid tumor or cancer is either a lung cancer or colon cancer.

116. (New) The method of claim 113 wherein the subject is a mammal.

117. (New) The method of claim 113 wherein the subject is a human.

118. (New) The method of claim 113, comprising administering an effective amount of cytoxan.

119. (New) The method of claim 113, comprising administering an effective amount of cisplatin.

REMARKS

Claims 100, 103, 106, 108 and 111-112 are pending. No claims are allowed.

Claims 100-112 have been canceled without prejudice. Applicants reserve the right to rejoin the canceled subject matter upon allowance of a generic claim.

New claims 113-119 are added by this amendment. It is believed that this amendment does not introduce new matter. Further, it is respectfully noted that new claims 113-118 are largely based on canceled claim 103, and therefore do not raise new issues.

Examiner's comments are addressed in sequence below.

Preliminary Comments

Applicants respectfully request that in the event that Examiner believes it is proper to maintain the final rejections that she will consider entering the amendment, and any exhibits attached thereto, into the record. It is respectfully submitted that the amendment and remarks, filed herewith, traverse the rejections and substantially narrow the issues should an appeal be filed. Further, it is believed that the new claims are in condition for allowance and/or simplify the issues and raise no new issues. MPEP 714.13 (II).

Further, the new claims do not add new matter. The amendment filed herewith cancels all finally rejected claims and presents new claims that, with the remarks below, are believed to overcome all rejections.

A. Rejections Under § 112,2nd Paragraph

Claims 100, 103, 106, 108, 111 and 112 are rejected for allegedly being vague and indefinite. Examiner asserts that the specification does not define what structure is required to meet the claim limitations, attenuated and particularly, tumor targeting.

A.1 "Attenuation"

With respect to attenuation, the claimed subject matter recites an inability to synthesize toxic LPS; i.e., endotoxin. Accompanying **Exhibit A** (5 pages) describes the biochemistry and pathophysiology of endotoxin's effects.

New claim 113 states that the tumor-targeted Salmonella comprises a msbB$^-$ mutation that is known to disrupt the formation of functional endotoxin. Col. 26, lines 25, *et seq.* It is respectfully submitted that the molecular structure conferring the attenuated phenotype is unambiguous.

Accordingly, Applicants respectfully request that this basis of rejection be withdrawn.

A.2 "Tumor-targeted"

With respect to the alleged indefiniteness of the claim limitation "tumor-targeted," it is set forth in MPEP 2173.02 that the definiteness of claim language must be analyzed, not in a vacuum, but in light of … the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. The rejection instead seems predicated on not knowing how the attenuated tumor-targeted Salmonella achieves it localization to tumors. However,

knowledge of the mechanism underlying an invention is not a statutory requirement for patentability.

The term "tumor-targeted" is a functional limitation describing a complex property of the bacterial vectors. It is precisely because some properties of an invention may not lend themselves to structural terms that functional limitations have been deemed appropriate as a definite and precise form of claim language. MPEP § 2173.05(g). The term "tumor-targeted" does not render the claims indefinite unless persons of ordinary skill in the art would not understand the scope of the claim. Respectfully, no evidence of this lack of understanding has been proposed.

The Office Action does not precisely state why the absence of a recited or disclosed structure that confers the tumor-targeted phenotype, would render the claim vague or indefinite to those in the art. It is respectfully submitted that persons of ordinary skill in this area of research would appreciate that a tumor-targeted phenotype is a complex phenotype that is not yet amenable to description in molecular terms or in structural terms.

Further, the wording of the rejection suggests that Examiner assumes that an easily discernible structure is what actually confers tumor-targeted behavior. It is respectfully noted that, to the best of our knowledge, no such evidence is available.

It is respectfully submitted that the claimed subject matter satisfies the statutory requirement of definiteness of claim language. As stated in MPEP § 2173.02, the essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree

of clarity and particularity. Definiteness of claim language must be analyzed, in light of the application disclosure, teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

It is respectfully suggested that the claims presented clearly meet the "reasonable degree" requirement. Therefore, it is respectfully requested that the rejection of the claims for allegedly being indefinite be withdrawn.

B. Rejection Under § 112, 1ST, Paragraph

Although Applicants do not concede the correctness of the rejection, the pending claims have been canceled and new claims 113-118 have been added. The new claims incorporate Examiner's suggestion regarding the msbB$^-$ Salmonella mutant.

It is respectfully submitted that the rejection under § 112, 1st paragraph, may be withdrawn.

C. Rejection Under 103(a)

Claims 100, 103,106, 108,111 and 112 are rejected for allegedly being obvious over Low et al., and Schachter et al. Applicants respectfully disagrees that Low or Schachter taken individually or in combination are sufficient to make a *prima facie* case of obviousness.

It is respectfully noted that Examiner states that her purpose in citing Low is to demonstrate that Low taught attenuated Salmonella biotherapy in treating cancer. Final Office Action, page 6, para. 2. Examiner asserts that "[t]he Office cited Schachter et al to show the need and motivation was present in

the art to combine chemotherapy with bio-therapy, one could use either the cytokine biotherapy as taught by Schachter et al, or the attenuated Salmonella biotherapy as taught by Low et al with a reasonable expectation of success for treating cancer. It was within the levels of the skilled in the art, and a matter of optimization to determine the proper dosing regimen so that the combined therapy would not lead to a detrimental effect."

Applicants respectfully disagree for the reasons set forth below.

C.1 The Schachter Reference

Schacter states that therapy using a single chemotherapeutic agent generally provides low responses, whereas a combination may result in a significantly higher response rate. Schachter, page 155, col. 2, to page 156, top of col 1. Therefore, Schachter's approach, in large part is based on his belief that a combination of drugs is better than a regimen comprising a single compound.

The goal of Schachter's work was "to design a combined chemo-biotherapy program" that would "achieve optimal tumor destruction by anti-cancer drugs on the one hand, and to induce systemic anti-tumor immunity by immunomodulators on the other." Schachter,page 156, col. 2. Thus, Schachter's approach was to employ Del Prete's combination of drugs with additional specific immunodulators. Schachter, page 156, top col. 1, discussing the Del Prete reference.

Of the immunomodulators discussed, Schachter uses IFN-α and GM-CSF in combination with a combination of drugs that provided an overall response rate of 44%. Schachter, page 156, top col. 1, discussing the Del Prete reference. By combining the combination of drugs with IFN-α and GM-CSF, the response of the combination

of drugs increased to ~50%. Schachter, Abstract. In other words, the combination of cytokines only marginally enhanced the effect of the combination of drugs of compounds.

C.2 Applicants' Invention

The newly added claims are directed to methods of inhibiting the growth or reducing the volume of a solid tumor by administering either cisplatin or cytoxan in conjunction with attenuated tumor-targeted Salmonella. Examiner's attention is respectfully directed to Figures 39-41 of the specification.

Figure 39 demonstrates that administering cytoxan in the absence of attenuated tumor-targeted Salmonella provides a marginal reduction in tumor volume. The reduction in volume observed when attenuated tumor-targeted Salmonella are used alone shows a greater reduction ~ 50%. However, when attenuated tumor-targeted Salmonella and cytoxan are used in combination, the decrease in tumor volume is > ~80%. This is evidence of synergism between the drug and the attenuated tumor-targeted Salmonella. If the effect were only additive, then the reduction would be ~55-60%.

Similar results are presented in Figure 41 for the combination of attenuated tumor-targeted Salmonella and cisplatin. The cisplatin-only treated animals and the control group died prior to the evaluation on day 40. However, these data are consistent with those in Fig. 39 in demonstrating that cisplatin in combination with the attenuated tumor-targeted Salmonella act synergistically in reducing tumor volume.

It is noteworthy that Fig. 40 illustrates that attenuated tumor-targeted Salmonella in combination with mitomycin C do not act synergistically. In fact, mitomycin C has negligible effect on

tumors either alone, or in enhancing the effectiveness of attenuated tumor-targeted Salmonella.

The fact that either cytoxan or cisplatin provide a synergistic response when combined with attenuated tumor-targeted Salmonella, whereas the third drug, mitomycin C does not, shows that the effectiveness of a combination therapy must be empirically determined and cannot be predicted with even a reasonable degree of certainty.

C.3 The Office Action Does Not Compare The Claimed Method With The Closest Available Art

During prosecution, Applicants may compare their claimed invention with prior art that is more closely related to the invention than the prior art relied upon by the examiner. MPEP § 716.02(e). In the present case Applicants respectively submit that comparing the claimed methods with cytoxan or cisplatin with the method using mitomycin C is far closer than the combined teachings of Schachter and Low.

The data in Figure 40 result from using the attenuated tumor-targeted Salmonella in combination with a different single chemotherapy compound, i.e., mitomycin C. This combination differs from the claimed methods in only one claim element, thereby the closest prior art possible; and far closer to the claims than the combination of Schachter and Low.

In this regard it is therefore important to note that mitomycin C has no substantial effect on tumor growth or volume when administered alone. But even more critical to this discussion is that mitomycin C does not provide any meaningful enhancement on the effectiveness of the attenuated tumor-targeted Salmonella.

See Fig. 40. Thus, this comparison provides closer prior art for the purposes of determining nonobviousness. It demonstrates that the effectiveness of the combination of the attenuated tumor-targeted Salmonella and a chemotherapy compound is not predictable. Accordingly, there cannot be a reasonable expectation of success in combining the teachings of far less relevant prior art such as Schacter/Low.

Applicants respectfully submit that the claimed methods do not have a reasonable expectation of success over the closest prior art. Accordingly, withdrawal of the rejection is respectively requested.

C.4 Schachter And Low Do Not Provide Any Basis For A Reasonable Expectation Of Synergism Between Attenuated Tumor-Targeted Salmonella And Cisplatin Or Cytoxan

"A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." In re Corkill, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.1989. MPEP 716.02(a).

The force of evidence of synergistic effects in support of a finding of nonobviousness is further strengthened when the prior art does not provide a basis to predict a supra-additive result. Id. The combination of Schachter/Low do not provide any basis to predict synergistic effects demonstrated.

The claimed methods illustrated in Figures 39 and 41 demonstrate a synergistic (greater than supra-additive) effectiveness between the attenuated tumor-targeted Salmonella and either of cisplatin or cytoxan. There is no disclosure in the combined teachings of Schachter and Low, together with knowledge in the art that would provide a reasonable expectation of this synergistic relationship. Although synergism may be found in the literature, results from many laboratories indicate that the interactions between chemotherapeutic agents must be empirically determined. See Exhibit A.

In accordance with the guidelines in MPEP 716.02(a), it is respectfully requested that the rejection be withdrawn.

C.5 The Rejection's Reliance on In re Kerkhoven is Improper

A comparison of the relevant facts here with those in Kerkhoven does not support invoking the rule of Kerkhoven in this matter. In Kerkhoven, the prior art presented five references disclosing specific formulations for various detergent compositions as well as the methods of making them. In Kerkhoven, the rejection was very specific in that all of the references described specific compositions and how to make them. In re Kerkhoven, 626 F.2d 846, 848-48, (CCPA 1980).

It should also be noted that the technical art dealt with in Kerkhoven is a far more predictable one than in the present case. For example, mixing two detergent compositions to form a third effective detergent composition has a far greater expectation of success than developing an effective combination cancer therapy. The Office Action asserts that "one could use either the cytokine biotherapy as taught by Schachter et al, or the attenuated

Salmonella biotherapy as taught by Low et al with a reasonable expectation of success for treating cancer." A major problem with this conclusion is that it does not take into consideration the unpredictability of effectiveness of combinations of chemotherapy agents.

There is no evidence in the cited references or in the art generally, to support the conclusion that attenuated tumor-targeted Salmonella plus either cytoxan or cisplatin may reasonably be expected to behave similar to, worse than or better than IFN-α and/or GM-CSF coupled with Del Prete's combined compounds. The Office Action simply groups the attenuated tumor-targeted Salmonella and IFN-α and/or GM-CSF under the same umbrella of "biotherapy," but does not address in specific scientific terms, why persons of ordinary skill in the art would reasonably expect the claimed method to be effective in view of the applied references.

For example, Schachter uses no bacterial vectors, nor does he even disclose them as a suitable alternative for IFN-α and/or GM-CSF. Further, Schachter employs IFN-α, followed by four chemotherapeutic agents -BCNU, CDDP, DTIC, and tamoxifen- followed by GM-CSF. See Treatment, p. 157. It remains to be explained how combining Schachter and Low would lead persons of ordinary skill in the art to the claimed method with a reasonable expectation of success.

Exhibit B (2 pages) is an abstract of a paper published by Chow, et al, provides data demonstrating that the known anticancer drug Ara-C, in combination with an additional anticancer drug 2-CdA, provides a synergistic inhibition of cancer cell lines in vitro. Leuk Lymphoma, (2003) 44(1): 165-73. In contrast, it is also

reported that combinations of Ara-C with either fludarabine or bendamustine yielded either antagonistic or additive inhibitory effects. These results establish that not all combinations of anticancer drugs provide a predictable effectiveness of inhibiting cancer cell growth.

Exhibit C (1 page) provides additional evidence supporting the conclusion that anticancer drug combinations are not typically expected to be effective is provided by Budman et al. Anticancer Drugs (2002) 13 (10): 1011-1016. In this report, the anticancer compound docetaxil was combined with one of 18 additional anticancer drugs, and the drug combination was subsequently tested for their effectiveness in inhibiting cell growth in 3 different prostate cancer cell lines. The results showed that docetaxil in combination with either doxorubicin or epirubicin can be expected to yield synergistic growth inhibitory effects.

In contrast, docetaxil in combination with either cisplatin, carboplatin or etoposide showed antagonistic growth inhibitory effects. Further, docetaxil combined with either of retinoic acid, cyclosporin A or vinorelbine yielded either additive or synergistic effects. In sum, it is respectfully suggested that examiner's belief that any combination of anticancer drugs would be expected to provide a beneficial growth inhibitory effects is inaccurate and not a proper basis for an obviousness rejection.

The experiments described above indicate that anticancer drug effects are largely based on empirical observation and cannot be reasonably predicted. The results of Dasmahapatra, et al., see **Exhibit D** (11 pages) further illustrate this point. Clinical Cancer Res. (2004) 10: 5242-5252. In this report, low concentrations of both of the anticancer compounds, perifosine

and UCN-01 were shown to be inactive in inhibiting the growth of two lung adenocarcinoma cell lines. Surprisingly, when perifosine and UCN-01 were combined and added to culture medium (within the same concentration ranges), cell growth was almost completely inhibited. Thus, beneficial and synergistic drug effects can occur between compounds that individually are without effect.

It is respectfully submitted that it would be very difficult to provide a rationale explaining how persons skilled in the art could have predicted the synergism exemplified by two inactive compounds. However, such a combination would be found to be obvious under the present mode of analysis.

In conclusion, examiner's statement that it is obvious for those skilled in the art to achieve a technical solution that is encompassed by the synergistic effects of two anticancer drugs is inaccurate. We provide here three reports clearly demonstrating that the effectiveness of combinations of chemotherapy agents cannot be predicted without the relevant empirical results.

Applicants respectfully request that the rejections under § 103(a) predicated on the Kerkhoven rationale and that fail to consider the unpredictability in the art be withdrawn.

C.6 Applicant's Claims Teach Away From Schachter

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). MPEP § 2141.02(VI). It is respectfully

submitted that the teachings and suggestions in Schacter would lead away from the claimed subject matter.

Schacter states that therapy using a single chemotherapeutic agent provides low responses, whereas a combination may result in a significantly higher response rate. Schachter, page 155, col. 2, to page 156, top of col 1. Therefore, Schachter's approach, in large part is due to his belief that a combination of drugs is better than individually administered compounds.

The goal of Schachter's work was "to design a combined chemo-biotherapy program" that would "achieve optimal tumor destruction by anti-cancer drugs on the one hand, and to induce systemic anti-tumor immunity by immunomodulators on the other." Schachter,page 156, col. 2. Thus, Schachter's approach was to employ Del Prete's combination of drugs of drugs with additional specific immunodulators. Schachter, page 156, top col. 1, discussing the Del Prete reference.

Of the immunomodulators discussed, Schachter uses IFN-α and GM-CSF in combination with a combination of drugs that provided an overall response rate of 44%. Schachter, page 156, top col. 1, discussing the Del Prete reference. By combining the combination of drugs with IFN-α and GM-CSF, the response of the combination of drugs increased to ~50%. Schachter, Abstract. Therefore, the combination of cytokines only marginally enhanced the effect of the combination of drugs of compounds.

In contrast, Applicants' specification discloses that only a single compound is necessary to synergize with the attenuated tumor-targeted Salmonella. In this case, the compound may be either cytoxan or cisplatin. It is virtually indisputable that

persons of ordinary skill in the art could not have reasonably expected such results based on Schachter's chemo/biotherapy that is based on Del Prete's regimen of four compounds.

Therefore, Examiner proposes a modification whereby Schachter's regimen of using four distinct compounds would necessarily be discard in favor of a regimen employing only one single compound. It is respectfully submitted that Applicants' claimed subject matter follows the opposite path taught by Schachter. In accordance with established practice, this is significant evidence of nonobviousness of the claimed subject matter. MPEP § 2141.02(VI). In view of Applicants taking a different path o research than Schachter teaches, it is respectfully requested that the rejection under § 103(a) be withdrawn.

Conclusion

It is respectfully suggested that in view of the amendments to the claims and the foregoing remarks that the application is in condition for allowance and that allowance is respectfully requested.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

Albert Wai-Kit Chan

Albert Wai-Kit Chan
Registration No. 36,479
Attorney for Applicant(s)
Law Offices of
Albert Wai-Kit Chan, LLC
World Plaza, Suite 604
141-07 20th Avenue
Whitestone, New York 11357
Tel: (718) 799-1000
Fax: (718) 357-8615
E-mail: chank@kitchanlaw.com